Remarks

In the official action of 29 February 2007, claims 1, 4-9, and 16-25 are pending and were examined. Claims 1, 4-9, and 16-25 remain rejected under 35 U.S.C. §103(a) as allegedly obvious. Claims 1, 4-9, 16-21, and 25 also remain rejected under a nonstatutory obviousness-type double patenting rejection as allegedly obvious.

Claims 1, 4-9, and 16-25 are pending after entry of this amendment. Claims 16-21 are amended to correct typographical errors that would be obvious to one of ordinary skill in the art. No new matter has been introduced as a result of the amendments herein. Reconsideration in view of the following remarks is respectfully requested. If the pending claims are not found to be in condition for allowance, the examiner is respectfully requested to contact the undersigned to schedule an interview before mailing an official action.

Rejection of claims 1, 4, 5, 7, 16, 18, 21 and 25 pursuant to 35 U.S.C. §103(a)

Claims 1, 4, 5, 7, 16, 18, 21 and 25 remain rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of Felberbaum et al. (1997) or Albano et al. (1996) or Engel et al. (1997) or Olivennes et al. (1994), in view of Ziegler et al. (1998) and Hall et al. (1991). Official action, pages 3-10.

The burden is on the examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co*., 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc*., 550 U.S. __, 82 USPQ2d 1385 (2007), the U.S. Supreme Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (USPTO Guidelines) state that, having undertaken the factual inquiries of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known

element for another to obtain predictable results; (3) use of a known technique to improve similar methods in the same way; (4) applying a known technique to a known method ready for improvement to yield predictable results; (5) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (6) variations that would have been predictable to one of ordinary skill in the art; and (7) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007).

Each of the above-noted rationales requires predictability in the art and/or a reasonable expectation of success, and the **examiner must consider objective evidence that rebuts such predictability and reasonable expectation of success**. The objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long-felt but unsolved needs, as found in the specification as-filed or other source. *Id*. When considering the obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at __, 82 USPQ2d at 1396. The applicants submit that the examiner fails to make a *prima facie* case because none of the cited references, either individually or taken together, are sufficient to render claims 1, 4, 5, 7, 16, 18, 21 and 25 obvious given that none of the rationales identified by the U.S. Supreme Court in *KSR* apply, and/or the objective evidence provided herein rebuts any alleged predictably or reasonable expectation of success.

(1) Combining prior art elements according to known methods to yield predictable results

Claim 1 (and remaining claims 4-9 and 16-25 depending therefrom) are directed to methods of programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART), the method comprising the following common steps:

a) programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle,

wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix, and further wherein the LHRH antagonist is administered at a dosage range between 0.5 mg to 10 mg;

b) terminating administration of the LHRH antagonist prior to the onset of menses;

c) programming controlled ovarian stimulation by stimulating ovarian follicle growth by administering a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof, during the follicular phase of the programmed menstrual cycle;

d) suppressing premature ovulation by administering a LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix during the follicular phase of the programmed menstrual cycle;

e) inducing ovulation by administering HCG; and

f) applying assisted reproduction techniques.

In the official action, the four alternative primary references (Felberbaum et al., Albano et al., Engel et al., and Olivennes et al.) are alleged to teach methods for the therapeutic management of infertility by stimulating ovarian follicle growth by administering a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof; suppressing premature ovulation by administering a LHRH antagonist during the follicular phase of a treatment cycle; inducing ovulation by administering HCG; and applying assisted reproduction techniques (*i.e.*, steps (c)-(f) of claim 1 or classical COS-ART techniques). Official action, pages 3-6.

However, as noted by the examiner, none of the primary references disclose programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding

menstrual cycle and terminating administration of the LHRH antagonist prior to the onset of menses (*i.e.*, steps 1(a) and 1(b)). Official action, top of page 6.

Ziegler et al is alleged to teach that the advanced timing of COH can be accomplished by administering a compound (oestradiol valerate) during the luteal phase to allow for advanced scheduling of treatments. Official action, page 7.

However, as **a)** oestradiol valerate is not an LHRH antagonist; **b)** the administration of oestradiol valerate, much less an LHRH antagonist, is not terminated prior to the onset of menses; and **c)** Ziegler et al. fail to disclose the suppression of premature ovulation by administering a LHRH antagonist during the follicular phase of the programmed menstrual cycle and inducing ovulation by administering HCG (*i.e.*, steps 1(e) and 1(f)), Ziegler et al. fail to disclose all elements of claim 1.

Hall et al is alleged to teach that administration of an LHRH antagonist in the mid-luteal phase results in luteolysis, termination of administration of an LHRH antagonist prior to menses, and a programmed menstrual cycle. Official action, page 7.

However, as **a)** Hall et al. describe induction in normal, as opposed to infertile, patients; **b)** an LHRH antagonist that is neither cetrorelix, teverelix, ganirelix, antide, nor abarelix; and **c)** Hall et al fail to describe any classical COS-ART procedures or a programmed menstrual cycle (*i.e.*, steps 1(c)-1(f)), Hall et al also fail to disclose all elements of claim 1.

When taken together, all elements of claim 1 are not in the prior art cited by the examiner. Even if they were, modifying classical COS-ART procedures as taught by the present invention would **not** yield predictable results based upon the teachings of the cited references.

As stated above, Ziegler et al is alleged to teach that the advanced timing of COH can be accomplished by administering a compound (oestradiol valerate) during the luteal phase. Official action, page 6. More generally, Ziegler et al is alleged to stand for the proposition that agents and methods can be utilized to time the onset of COH treatments and that such advanced timing is desirable to allow for better scheduling. Official action, page 17.

With respect to this latter part of Ziegler et al's alleged general proposition, the applicants acknowledge that it was known prior to the present invention that classical COS/ART procedures had room for desirable improvements and that skilled artisans in the field were motivated to achieve these desirable improvements. In this respect, Ziegler et al really say nothing more than is stated by the application, and in a greater sense, the same can be said of any field. All inventions, technologies, and solutions have weaknesses, shortcomings, and room for improvement and skilled artisans seek and develop new solutions to these problems.

With respect to the former part of Ziegler et al's alleged general proposition, the applicants must disagree with the examiner's characterization. A skilled artisan would understand that Ziegler et al describe an **alternative** to classical COS/ART procedures that eliminates elements that add cost, complexity and inconvenience ("[o]ur procedure…provides the practical advantage of permitting the advanced timing of the onset of COH when gonadotropin-releasing hormone (a.k.a. LHRH) agonists are not used" and "provides the same practical advantages without the complexity, the cost and the increased risk of ovarian hyperstimulation inherent in the use of GnRH agonists"; *see* Abstract and page 563, left hand column, lines 9-15).

Consistent with their stated objectives, Ziegler et al administer oestradiol valerate to test subjects to synchronize the exogenous and endogenous FSH stimuli in COH and "provide a more physiological approach to multiple follicular stimulation and possibly improve the quality of COH and its outcome while diminishing the overall need for HMG or recombinant FSH." (*see* page 562, left hand column, lines 33-37).

As such, a skilled artisan would consider administration of an additional compound during the luteal phase in accordance with the claimed methods as contrary to Ziegler et al's protocol (*i.e.*, an additional compound would add complexity and cost, and even more so given that the claimed methods require an LHRH antagonist and HCG, as opposed to an LHRH agonist, to be administered during the follicular phase of the programmed cycle).

Furthermore, as described above, Ziegler et al teach the skilled artisan to administer oestradiol valerate in the luteal phase and continue administration of the compound through the

onset of menses. Ziegler et al **do not** teach the skilled artisan to administer LHRH antagonists in the luteal phase and terminate administration of the compound prior to menses. Therefore, the procedure of Ziegler et al has no effect on the timing of menses, while the presently claimed methods do. The induction of menstrual bleeding is crucial to the presently claimed methods because the start of menses allows a skilled artisan to accurately calculate the duration of the growth of follicles/oocytes and hence the timing of oocyte pick-up and transfer. **This alone demonstrates why Ziegler et al cannot be considered to teach that advanced timing of any and all COS/ART procedures can be accomplished by administering any compound during the luteal phase**, much less those methods in accord with the present invention.

In further support of this position, the applicants point out that while Ziegler et al's procedure allegedly reduces the complexity and cost of classical COS/ART methods, the teaching away from, and absence of, steps 1(d) and 1(e) of the claimed methods renders Ziegler et al's procedure unable to protect against premature ovulation (*see* page 563, left hand column, lines 15-17). **Premature ovulation defeats the purpose of programming an infertility treatment cycle**.

However, even if a skilled artisan were motivated to modify Ziegler et al *contrary to its teachings* to attempt to overcome this disadvantage by incorporating an LHRH agonist or steps 1(d) and 1(e) into the follicular phase of Ziegler et al's procedure, **this modification would still fail to render the claimed methods obvious** because prior to present invention it was unknown whether altering endocrine hormone balance by administering an LHRH antagonist in the luteal phase immediately preceding a programmed infertility treatment cycle would impact ovarian stimulation and reproductive endocrine feedback mechanisms in infertile patients in the subsequent menstrual cycle and beyond. (*i.e.*, it was unknown whether carrying out steps 1(a) and 1(b) would impact steps 1(d) and 1(e) such that the goal of the methods as described and claimed could actually achieve their intended purpose). In view of this knowledge, a skilled artisan would understand that any conclusions regarding the effects of administering oestradiol valerate in the luteal phase have **no bearing** on the effects of administering an LHRH antagonist in the luteal phase with respect to COS/ART procedures. They are different compounds and

have completely different effects in the female reproductive system. **For these reasons a skilled artisan would not apply the teachings of Ziegler et al to the teachings of the primary references because they are contradictory in nature (*i.e.*, there is no motivation to combine the references)**.

Having addressed Ziegler et al by itself, the applicants acknowledge that the combined teachings of the primary references and Ziegler et al still have to be addressed in view of the teachings of Hall et al.

As previously discussed, Hall et al is alleged to disclose **a)** that administration of an LHRH antagonist in the mid-luteal phase results in luteolysis; **b)** termination of administration of an LHRH antagonist prior to menses; and **c)** a programmed menstrual cycle. Official action, page 7. More generally, Hall et al is alleged to stand for the proposition that the menstrual cycle can be controlled with GnRH antagonists. Official action, page 18.

Contrary to the examiner's allegations, Hall et al **does not** in any way disclose a programmed menstrual cycle that even remotely resembles a programmed infertility treatment cycle according to the present invention. For example, Hall et al's studies are not performed on infertile subjects and Hall et al lack any data concerning their observations in the context of COS/ART procedures. Thus, while Hall et al may demonstrate that certain facets of the menstrual cycle may be affected by GnRH antagonists (*e.g.*, luteolysis can be induced by GnRH antagonist administration in the luteal phase), Hall et al fail to demonstrate that a menstrual cycle can be programmed in accordance with the claimed methods (*i.e.*, that GnRH antagonists can be administered in the luteal phase preceding a programmed infertility treatment cycle **without** affecting the COS/ART procedures in the follicular phase of the programmed cycle).

In fact not only do Hall et al fail to describe a programmed cycle in accordance with the claimed methods, **Hall et al demonstrate the opposite** (*i.e.*, the administration of GnRH antagonists in the luteal phase affects the subsequent menstrual cycle). For example, with respect to their MLP studies, Hall et al state "[t]he cycle following antagonist-induced luteolysis was longer than the vehicle control cycle. Further study will be required to determine whether

this difference is the result of altered gonadatropin dynamics…and possible effects on the developing follicle" (*see* page 999, left hand column, lines 18-23).

These observations are consistent with would be expected by the skilled artisan prior to disclosure of the present invention. For example, prior to the present invention, LHRH antagonists were considered to be capable of compromising the mitotic program of cells undergoing folliculogenesis, blastomere formation and endometrium development by inhibiting the synthesis of growth factors and through direct interactions with the LHRH receptor (*e.g.*, *see* the abstract of Hernandez, 2000, *Human Reproduction* 15(6):1211-1216). LHRH antagonists were also considered to be capable of interfering with mechanisms involved in germinal vesicle breakdown and the cell signaling pathway driving the oocyte into metaphase II (*e.g.*, *see* De la Fuente et al, 1999, *Human Reproduction* 14: 3060-3068).

In other words, a skilled artisan reading Hall et al would conclude from the observed alteration in cycle length that the administration of Nal-Glu (or other LHRH antagonist) in the luteal phase results in a disturbance of reproductive hormones and/or endocrine feedback mechanisms in the subsequent menstrual cycle.

Such an induced hormonal disturbance would be counterproductive to any attempt to improve the timing of oocyte pick-up and transfer. Furthermore, the skilled artisan would have no idea how this induced hormonal disturbance would affect the administration of other hormones in the subsequent menstrual cycle (*i.e.*, steps 1(c)-1(f)). As such, in view of Hall et al, the skilled artisan seeking to improve classical COS/ART techniques would **not** administer Nal-Glu or any other LHRH antagonist in the luteal phase immediately preceding the programmed cycle. Instead a skilled artisan would expect that administration of an LHRH antagonist during the luteal phase in an amount sufficient to induce luteolysis and the start of menses would have deleterious effects on oocyte meiosis and the mitotic programs of cells undergoing folliculogenesis, blastomere formation and endometrium development during the following cycle. This does not even take into account the fact that Hall et al are examining women with normal, as opposed to infertile, patients, as many infertile patients may suffer from hormonal

imbalances that require further consideration. In this regard, Hall et al can be considered to *teach away* from the claimed methods.

In the official action, the examiner reiterates a previous rebuttal by alleging that the primary references demonstrate that GnRH or LHRH antagonists are safe and effective for use with assisted reproductive techniques. Official action, page 19. However, the applicants reiterate that **none of the cited references, including the primary references, disclose or suggest that LHRH antagonists can be administered during the luteal phase of the preceding menstrual cycle in a manner that does not impact COS/ART procedures performed in the subsequent menstrual cycle, much less to infertile women. Notably, the examiner fails to acknowledge or contradict this point in the official action.**

All the primary references disclose the administration of LHRH antagonists **during the follicular phase**, which is not surprising given that administration of LHRH antagonists during the follicular phase is part of many classical COS/ART procedures. In view of Hall et al and the body of knowledge concerning LHRH antagonists, a skilled artisan **could not** conclude that administration of an LHRH antagonist in the luteal phase preceding any classical COS/ART procedure would work in the way demonstrated by the present application. Thus, the claimed methods would not and could not have been predicted by a skilled artisan.

For these reasons, the applicants believe that the first rationale of the *Examination Guidelines* does not apply. With respect to the other rationales provided in the *Examination Guidelines*, Ziegler et al and Hall et al are discussed further below.

(2) Simple substitution of one known element for another to obtain predictable results

It **cannot** be said that the claims are directed to methods that are a mere simple substitution of elements from the prior art, because not all of the elements of the claimed methods were present in the prior art. Furthermore, given that the teachings of Hall et al are consistent with and reinforce the knowledge in the art (*i.e.*, LHRH antagonist administration during the luteal phase would be expected to upset hormonal balance and endocrine feedback mechanisms in the subsequent menstrual cycle in a manner incompatible with programming the

cycle to better and more accurately time oocyte pickup and transfer), the methods of the present application would certainly be viewed as surprising, unpredictable, and counterintuitive in view of the prior art. For these reasons the applicants believe that the second rationale of the *Examination Guidelines* does not apply.

(3) Use of a known technique to improve similar methods in the same way

The examiner alleges that the primary references disclose steps 1(c)-1(f) of claim 1, but acknowledges that the primary references fail to disclose steps 1(a) and 1(b). As set forth above, a skilled artisan might view Hall et al's as teaching *inter alia* that a GnRH antagonist can induce menses, but the skilled artisan would not seek to combine that with classical COS/ART techniques given that Hall et al demonstrates that administration of an LHRH antagonist in the luteal phase upsets hormonal balance and/or endocrine feedback mechanisms in the subsequent menstrual cycle in a manner inconsistent with programming a cycle to improve oocyte pickup and transfer. Ziegler et al are not seeking to improve similar methods in the same way, as clearly Ziegler et al seek to eliminate elements of classical COS/ART procedures with their purported benefits and notable shortcomings (described above). Furthermore, this rationale requires that a skilled artisan have a reasonable expectation of success, which based upon the above analysis is clearly lacking. For these reasons the applicants believe that the third rationale of the *Examination Guidelines* does not apply.

(4) Applying a known technique to a known method ready for improvement to yield predictable results

As described in the preceding paragraph, a skilled artisan might view Hall et al as teaching *inter alia* that a GnRH antagonist can induce menses, and classical COS/ART procedures were known in the art. However, applying Hall et al's alleged teaching to classical COS/ART procedures in order to improve the accuracy of the timing of occyte pickup and transfer would be contraindicated based upon the demonstrated effects of luteal LHRH antagonist administration on the subsequent menstrual cycle. As discussed previously, in view

of the prior art and Hall et al (which are consistent with one another in this respect) a skilled artisan would expect luteal LHRH administration to do just what Hall et al showed. The present application defied the common sentiment evident in the art at the time of filing and surprisingly and unexpectedly demonstrated that luteal LHRH administration and termination prior to menses could be applied to classical COS/ART procedures and achieve the long-felt need to improve accuracy in oocyte pickup and transfer. In short, the results embodied by the claimed methods are unpredictable in view of the prior art. For these reasons, the applicants believe that the fourth rationale of the *Examination Guidelines* does not apply.

(5) Choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success

The examiner correctly notes that none of the primary references teach programming the start of controlled ovarian stimulation by administering an LHRH antagonist during the luteal phase of the menstrual cycle immediately preceding programmed menstrual cycle and terminating the administration of the LHRH antagonist prior to the onset of menses (*i.e.*, steps (a)-(b) of claim 1). Thus, in order for the claimed inventions to be obvious under this rationale, these additional elements would have to be chosen from a finite number of identified predictable solutions with a reasonable expectation of success.

For the reasons discussed above, there simply were no identified predictable solutions arising from the prior art cited by the examiner as could be applied to the improvement of classical COS/ART procedures. The solution(s) embodied by the claimed methods is counterintuitive and runs contrary to the prior art cited. Accordingly, the applicants believe that the fifth rationale of the *Examination Guidelines* does not apply.

(6) Variations that would have been predictable to one of ordinary skill in the art

Even if the claimed methods were viewed as a variation of classical COS/ART procedures, the claimed "variations" certainly would not have been predictable given that the luteal LHRH administration preceding a programmed infertility treatment cycle is

contraindicated absent the teachings of the present application. As stated before, the present application surprisingly and unexpectedly demonstrated that luteal LHRH administration preceding a programmed infertility treatment cycle could be safely accomplished in a manner consistent with the objective of improving classical COS/ART procedures. For these reasons, the applicants believe that the sixth rationale of the *Examination Guidelines* does not apply.

(7) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention

As discussed previously, there would be no teaching, suggestion or motivation to combine either one of Ziegler et al or Hall et al with the primary references in order to attempt to arrive at the claimed methods. Ziegler et al teaches away from classical COS/ART procedures by seeking to eliminate extra costly and complex steps. As a result, Ziegler et al's procedure is unable to protect against premature ovulation. Premature ovulation defeats the purpose of modifying classical COS/ART procedures in order to improve the accuracy of timing of oocyte pickup and transfer. Hall et al reinforce the knowledge in the art prior to the disclosure of the present application that administration of LHRH antagonists in the luteal phase of a menstrual cycle upset hormonal balance and/or endocrine feedback mechanisms in the subsequent cycle. These types of disturbances would be inconsistent with attempting to program that subsequent menstrual cycle in order to improve timing of oocyte pickup and transfer.

Based upon the foregoing, the applicants believe that the seventh rationale of the Examination Guidelines does not apply to the claimed methods. Further, the applicants assert that, prior to the present invention, the subject matter of claims 1, 4, 5, 7, 16, 18, 21 and 25 was neither described or could be reasonably predicted by one skilled in the art. Thus, the examiner has not established a *prima facie* case of obviousness. Withdrawal of the rejection of claims 1, 4, 5, 7, 16, 18, 21 and 25 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. is respectfully requested.

Rejection of claims 22 and 24 under 35 U.S.C. §103(a)

Claims 22 and 24 remain rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of in view of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. as applied to claims 1, 4, 5, 7, 10, 11, 16, 18, and 21-25, and in further view of U.S. Patent No. 5,470,847 to Garfield et al. Official action, page 11.

Other than Garfield et al, the references the examiner cites in support of these alleged rejections have been previously discussed. The examiner alleges that Garfield et al teach that clomiphene is a non-steroidal antiestrogen that stimulates ovulation by stimulating follicle growth and maturation. Official action, page 11.

Even if this were true, Garfield et al fails to overcome the deficiencies of the other prior art references. That is to say, in view of all these prior art references, a skilled artisan would **not** administer an LHRH antagonist to an infertile patient in the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle given the evidence prior to the disclosure of the present application that such administration results in hormonal disturbances and that prior to disclosure of the present application there was **no** demonstration in the art that LHRH antagonists could be administered to an infertile patient in the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle and successfully achieve the aims of the claimed methods, much less those of classical COS/ART procedures. A skilled artisan would not expect a different result by choosing to use clomiphene to stimulate ovarian follicle growth in an attempt to improve classical COS/ART procedures as contemplated by the present invention.

As such, prior to the present invention, the subject matter of claims 22 and 24 was neither described or could be reasonably predicted by one skilled in the art. Thus, the examiner has not established a *prima facie* case of obviousness of claims 22 and 24. Withdrawal of the rejection of claims 22 and 24 under 35 U.S.C. §103(a) as allegedly unpatentable over the combination of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. and in further view of Garfield et al is respectfully requested.

Rejection of claims 6, 8, 9, 17, 19, and 20 under 35 U.S.C. §103(a)

Claims 6, 8, 9, 17, 19 and 20 remain rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of in view of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. as applied to claims 1, 4, 5, 7, 10, 11, 16, 18, and 21-25, and in further view of U.S. Patent No. 5,945,128 to Deghengi or Rabasseda (1999). Official action, page 12.

Other than the Deghengi et al and Rabasseda et al, the references the examiner cites in support of these alleged rejections have been previously discussed. The examiner alleges that Deghengi teach that cetrorelix, teverelix, ganirelix, and antide were known to be the LHRH antagonists prior to the filing date of the application and that Rabasseda et al teach that LHRH antagonists such as cetrorelix, ganirelix, and abarelix were known to be useful for treating female infertility prior to the filing date of the application. Official action, pages 12-13.

Even if these alleged teachings were true, both Deghengi et al and Rabasseda et al fail to overcome the deficiencies of the other prior art references. That is to say, in view of all these prior art references, a skilled artisan would **not** administer an LHRH antagonist to an infertile patient in the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle given the evidence prior to the disclosure of the present application that such administration results in hormonal disturbances and that prior to disclosure of the present application there was **no** demonstration in the art that LHRH antagonists could be administered to an infertile patient in the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle and successfully achieve the aims of the claimed methods, much less those of classical COS/ART procedures. Notwithstanding the disclosed compounds' use in classical COS/ART procedures, one of ordinary skill in the art would have **no** motivation to administer any LHRH antagonist during the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle and in fact would be motivated against doing so.

Accordingly, the examiner has not established a *prima facie* case of the obviousness of claims 6, 8, 9, 17, 19 and 20. Withdrawal of the rejection of claims 6, 8, 9, 17, 19 and 20 under 35 U.S.C. § 103(a) as allegedly unpatentable over the combination of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in view of Ziegler et al. in further view of Hall et al. and in further view of Deghengi or Rabasseda is respectfully requested.

Rejection of claims 1, 4-9, 16-21 and 25 under Obviousness-Type Double Patenting

Claims 1, 4-9, 16-21 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 ("the '192 patent") of Engel et al., in view of Ziegler et al., Hall et al., Deghengi, Rabasseda, and U.S. Patent No. 4,016,259 to Kent.

In order to make a non-statutory obviousness-type double patenting rejection, the '192 patent and instant application must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement. 35 U.S.C. §§103(c)(2) and (c)(3). Further, the claimed subject matter must either be anticipated by, or merely an obvious variation of, the subject matter claimed in the '192 patent.

With respect to this latter requirement, the examiner alleges claims 1, 4-9, 16-21 and 25 are obvious variants of claims 1-6 of the '192 patent. Official action, pages 14-15. As such, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination. MPEP 804. Specifically, the examiner alleges that the claims of U.S. Patent No. 6,319,192 and the instant application only differ in that the instant claims set forth a programming step, and that in view of the alleged teachings of the prior art previously discussed, the instant claims would be obvious to one of ordinary skill in the art at the time of filing.

Both the '192 patent and present application have at least one common inventor and are commonly owned. Claims 1-6 of the '192 patent encompass methods of therapeutic management of infertility by intrauterine insemination consisting of dose-dependent suppression of endogenous gonadotropins with an LHRH antagonist, exogenous stimulation of ovarian

follicle growth, ovulation induction with HCG, native LHRH, LHRH agonists or recombinant LH, and intrauterine insemination by sperm injection.

However, the present claims 1, 4-9, 16-21 and 25 encompass methods of programming an infertility treatment cycle comprising controlled ovarian stimulation (COS) and assisted reproductive techniques (ART), the method comprising the following steps:

a) programming the start of a programmed menstrual cycle by inducing luteal regression in an infertile patient by administering an LHRH antagonist during the luteal phase of the preceding menstrual cycle,

wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix, and further wherein the LHRH antagonist is administered at a dosage range between 0.5 mg to 10 mg;

b) terminating administration of the LHRH antagonist prior to the onset of menses;

c) programming controlled ovarian stimulation by stimulating ovarian follicle growth by administering a compound selected from the group consisting of urinary FSH, recombinant FSH, HMG, recombinant LH, clomiphene, or a combination thereof, during the follicular phase of the programmed menstrual cycle;

d) suppressing premature ovulation by administering a LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix during the follicular phase of the programmed menstrual cycle;

e) inducing ovulation by administering HCG; and

f) applying assisted reproduction techniques.

As noted by the examiner, the claims of the '192 patent fail to set forth any programming steps (*i.e.*, programming the start of a programmed menstrual cycle and controlled ovarian stimulation). Furthermore, in view of the prior art cited, it would **not** be obvious for a skilled artisan to administer an LHRH antagonist to an infertile patient in the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle given the evidence prior to the disclosure of the present application that such administration results in hormonal disturbances and that prior to disclosure of the present application there was **no** demonstration in the art that

LHRH antagonists could be administered to an infertile patient in the luteal phase of a menstrual cycle immediately preceding a programmed infertility treatment cycle and successfully achieve the aims of the claimed methods, much less those of classical COS/ART procedures. In fact, a skilled artisan would be motivated against attempting to modify classical COS/ART procedures as taught by the present application given the effects of luteal LHRH antagonist administration demonstrated by Hall et al (and consistent with other prior art).

Accordingly, withdrawal of the rejection of claims 1, 4-9, 16-21 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 of Engel et al., in view of Ziegler et al., Hall et al., Deghengi, Rabasseda, and Kent is respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that claims 1, 4-9, 16-21 and 25 are in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that she feels may be best resolved through a personal or telephone interview, she is kindly requested to contact the undersigned attorney at the telephone number listed below. Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

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